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# Consistency Evaluation of the Dissolution of Generic and Original Preparations of Baclofen Tablets

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## ABSTRACT

**Introduction**: Baclofen tablets, a first-line drug for relieving muscle spasticity in neurological disorders, exhibit medium-dependent dissolution behavior, which may affect bioavailability and clinical efficacy. To ensure the reliability of dissolution testing and the consistency between generic baclofen tablets and the reference listed drug (RLD), this study focused on method validation for dissolution determination across multiple media and subsequent dissolution curve comparison. **Methods**: First, method validation for baclofen tablet dissolution determination was conducted using five dissolution media: 0.1 mol/L hydrochloric acid solution (HCl), 0.01 mol/L HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water. Validation parameters included specificity, linearity, filter membrane adsorption, accuracy, precision, robustness, and solution stability, following relevant guidelines. Subsequently, four of the above media (excluding water) were selected to compare the dissolution curves of three batches of generic tablets and three batches of RLD. The paddle method (50 rpm) was adopted for dissolution testing, and high-performance liquid chromatography (HPLC, detection wavelength: 265 nm) was used to determine cumulative dissolution rates at different time points; similarity was evaluated by calculating the $f_2$ factor. **Results**: The dissolution determination method passed all validation requirements in the five media: specificity was acceptable, linearity was acceptable, filter membrane adsorption was negligible, accuracy was acceptable, precision was reliable, robustness was satisfactory, and solutions remained stable for 24 hours. In the four media for curve comparison, both generic and RLD tablets showed rapid dissolution in acidic media (≥ 85% cumulative dissolution at 15 minutes); in pH 4.5 acetate buffer and pH 6.8 phosphate buffer, the mean cumulative dissolution difference between the two were ≤ 10% (5 mins) and ≤ 5% (≥ 10 mins), with $f_2$ values confirming dissolution curve similarity. **Conclusion**: The established HPLC method is reliable for baclofen tablet dissolution testing. Generic preparations and RLD show similar dissolution curves across media, supporting their in vitro equivalence. This provides a basis for ensuring clinical consistency of generics, thereby improving drug accessibility for patients with neurological spasticity.

**Keywords**: Baclofen tablets, original preparation, generic preparation, dissolution curve, consistency evaluation

## INTRODUCTION

Globally, neurological disorders accompanied by muscle spasticity—such as spinal cord injury, multiple sclerosis, and cerebral palsy—remain a major health challenge, seriously impairing motor function and quality of life for these patients (*1*–*4*). Within the comprehensive management strategies for these conditions, central muscle relaxants play a pivotal role, especially for long-term relief of spasticity-related symptoms in patients with persistent neurological damage (*5*, *6*). Baclofen tablets, a first-line clinical drug in this field, contain the active ingredient baclofen, a γ-aminobutyric acid (GABA) B receptor agonist (*7*, *8*). It binds to GABA B receptors on spinal anterior horn motor neurons and interneurons, inhibiting the release of excitatory neurotransmitters and reducing spinal nerve impulse conduction—thereby effectively alleviating muscle stiffness, spasms, and associated pain, and demonstrating significant clinical value in promoting patient rehabilitation (*9*–*12*).

As an oral solid dosage form with medium-dependent solubility, baclofen exhibits notably different dissolution behaviors across various media. Studies indicate that baclofen achieves rapid and complete dissolution in acidic media (e.g., 0.1 mol/L hydrochloric acid [HCl]) but shows slower and more variable release in neutral media (e.g., water) (*13*, *14*). This medium-dependent dissolution profile suggests that the bioavailability of baclofen formulations may be substantially influenced by variations in patients' gastrointestinal environments—such as changes in gastric acid concentration caused by age or concurrent medication—potentially leading to fluctuations in clinical efficacy (*15*). Therefore, evaluating the dissolution curve similarity between generic and original preparations of baclofen tablets is crucial to ensuring consistent and reliable therapeutic outcomes.

Currently, quality standards for baclofen tablets are included in six pharmacopoeias, namely the *Chinese Pharmacopoeia* (ChP), *United States Pharmacopeia* (USP), *British Pharmacopoeia* (BP), *Japanese Pharmacopoeia* (JP), *Korean Pharmacopoeia* (KP), and *Indian Pharmacopoeia* (IP) (*16*, *17*). All six pharmacopoeias uniformly adopt the paddle method for dissolution testing, with a consistent rotational speed of 50 rpm; however, significant differences exist in key dissolution parameters.

Based on existing international guidelines and pharmacopoeial requirements, this study established a high-performance liquid chromatography (HPLC)-based method to assess the in vitro dissolution profiles of baclofen tablets in media of varying pH levels. The aim was to compare generic preparations and the original research drug (RLD), providing a reference for dissolution curve analysis in bioequivalence (BE) studies.

This research contributes to the consistency evaluation of baclofen tablets, supporting the development of clinically equivalent generic alternatives with predictable therapeutic performance—ultimately improving drug accessibility and safeguarding the treatment needs of patients with neurological spasticity.

# METHODS

## Chemicals and Reagents

Generic baclofen tablets were sourced from Fuan Pharmaceutical Group Ningbo Team Pharmaceutical, Co., Ltd. (batch 190803 [BE batch], 190804, and 190805; expiration Aug 2023). The original preparations were supplied by Novartis Farma S.p.A. (batch TL641, TM629 [BE batch], and TV911; expiration Nov 2022). The reference substance of baclofen (batch 100928-200701, purity 99.4%) was obtained from the National Institutes for Food and Drug Control to ensure the accuracy of quantitative analysis.

HPLC-grade methanol, a key reagent for chromatographic analysis, was purchased from TEDIA. Analytical reagent-grade chemicals, including HCl, sodium acetate, acetic acid, potassium dihydrogen phosphate, sodium hydroxide, and sodium pentane sulfonate, were provided by National Pharmaceutical Group Chemical Reagent Co., Ltd. All solvents and reagents were used directly without additional purification steps to avoid introducing potential impurities that might interfere with the experiment. Ultrapure water required for solution preparation was produced using an Arium Comfort II purification system (Sartorius), meeting the water quality standards for pharmaceutical analysis.

Two electronic balances (XP26 and XS205DU, Mettler Toledo International Co., Ltd.) were used for weighing reagents and samples.

## Dissolution Method Selection

To establish a scientifically sound and pharmacopoeia-compliant dissolution method for baclofen tablets, a comprehensive review of quality standards was first conducted across major international pharmacopoeias, including the *Chinese Pharmacopoeia* (ChP), *United States Pharmacopeia* (USP), *British Pharmacopoeia* (BP), *Japanese Pharmacopoeia* (JP), *Korean Pharmacopoeia* (KP), and *Indian Pharmacopoeia* (IP). Detailed specifications are summarized in Table 1.

A comparative analysis of these standards revealed distinct analytical approaches: while the JP and KP adopt non-HPLC techniques for dissolution determination, the ChP, USP, BP, and IP uniformly specify HPLC as the preferred method for baclofen quantification. Considering the low content specification of baclofen tablets and the need for acceptable detection accuracy, the HPLC method was selected as the core analytical technique. Further parameter optimization confirmed that a dissolution medium volume of 500 mL (consistent with ChP, USP, JP, and KP) and a rotational speed of 50 rpm (uniformly recommended across all six pharmacopoeias) could ensure stable and reproducible dissolution behavior, avoiding issues such as incomplete drug release or overly rapid dissolution caused by inappropriate parameter settings.

The solubility of baclofen in each dissolution medium at 37 °C (0.01 mol/L HCl, 0.1 mol/L HCl, pH 4.5 acetate buffer, water, and pH 6.8 phosphate buffer medium) was investigated.

*Table 1. Comparison of Six Dissolution Methods for Baclofen Tablets*

| | ChP | USP | BP | JP | KP | IP |
|---|---|---|---|---|---|---|
| Dissolution apparatus and speed | Paddle, 50 rpm | Paddle, 50 rpm | Paddle, 50 rpm | Paddle, 50 rpm | Paddle, 50 rpm | Paddle, 50 rpm |
| Medium | 0.1 mol/L HCl | 0.01 mol/L HCl | 0.1 mol/L HCl | Water | Water | 0.1 mol/L HCl |
| Volume | 500 mL | 500 mL | 900 mL | 500 mL | 500 mL | 900 mL |
| Detection method and wavelength | HPLC, 265 nm | HPLC, 265 nm | HPLC, 265 nm | UV, 220 nm | UV, 220 nm | HPLC, 266 nm |
| Sampling time | 30 min | 30 min | 45 min | 45 min | 45 min | 45 min |
| Standard (% Dissolved) | ≥ 80% | ≥ 75% | ≥ 70% | ≥ 70% | ≥ 70% | ≥ 70% |

*ChP: Chinese Pharmacopeia; USP: United States Pharmacopeia; BP: British Pharmacopeia; JP: Japanese Pharmacopeia; KP: Korean Pharmacopeia; IP: Indian Pharmacopeia; HCl, hydrochloric acid solution; HPLC: high-performance liquid chromatography; UV: ultraviolet.*

The paddle method, a well-validated technique for oral solid dosage form dissolution testing, was employed to simulate in vivo gastrointestinal motility. The speed of the paddle was fixed at 50 rpm to maintain consistent hydrodynamic conditions. Dissolution tests were performed under strictly controlled conditions using a fully automatic intelligent dissolution meter (Agilent 708-805DS). The temperature of the dissolution medium was maintained at 37 ± 0.5 °C to mimic the human body temperature, and four types of dissolution media (0.01 and 0.1 mol/L HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) were used to simulate the pH gradient of the human gastrointestinal tract. This multimedia design ensured that the in vitro dissolution results comprehensively reflect the in vivo drug release behavior of baclofen tablets under different physiological environments.

After dissolution, the concentration of baclofen in the medium was quantified via HPLC at 265 nm. This wavelength was selected based on baclofen's ultraviolet (UV) absorption characteristics, ensuring acceptable sensitivity and specificity for target compound detection.

The cumulative dissolution rate of each tablet was calculated based on the HPLC quantitative results, and the similarity of dissolution curves between generic and original preparations was evaluated using the similarity factor ($f_2$) to assess the consistency of their in vitro drug release profiles.

**High-Performance Liquid Chromatography (HPLC) Conditions**

The HPLC conditions were optimized to achieve efficient separation and accurate detection of baclofen using an Agilent 1260 system. The chromatographic column used octadecylsilane-bonded silica gel as the stationary phase (4.6 × 250 mm, 5 μm); columns with equivalent performance could also be used to ensure method reproducibility.

The mobile phase was a mixture of three components: 0.3 mol/L glacial acetic acid solution, methanol, and 0.36 mol/L sodium pentanesulfonate solution, with a ratio of 550:440:20 v/v/v. This mobile phase composition was optimized to avoid peak tailing and ensure acceptable separation between baclofen and potential impurities.

An UV detector was used with a detection wavelength of 265 nm. The flow rate of the mobile phase was maintained at 1.0 mL/min, and the column temperature was controlled at 30 °C to stabilize the chromatographic system. The injection volume of the sample solution was 50 µL, which balanced the requirements of detection sensitivity and sample usage.

**Solution Preparation**

Four types of dissolution media were prepared in accordance with the ChP to simulate different physiological environments in the human gastrointestinal tract. The media included 500 mL each of 0.01 mol/L HCl, 0.1 mol/L HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer.

During the preparation process, the concentration and pH value of each medium were strictly controlled (Mettler Toledo Five Easy Plus FE28 pH meter). The pH of the acetate buffer was adjusted to 4.5 using acetic acid and sodium acetate; the pH of the phosphate buffer was adjusted to 6.8 using potassium dihydrogen phosphate and sodium hydroxide. All media were prepared using ultrapure water and were degassed before use to eliminate air bubbles that might affect dissolution results.

**Method Validation**

To verify the reliability and applicability of the established dissolution determination method, method validation was conducted in accordance with the guidelines of the International Council on Harmonization (ICH), covering eight key aspects: filter membrane adsorption, specificity, linearity, range, accuracy, precision, robustness, and solution stability. Each validation item was designed to address potential risks that might affect the experimental results, ensuring the method met the technical requirements for pharmaceutical analysis.

***System Suitability***

System suitability testing was performed to confirm the performance of the HPLC system. Approximately 20 mg of the baclofen reference substance was accurately weighed and placed in a 50-mL volumetric flask. To prepare the reference solution for each medium, 0.01 mol/L HCl, 0.1 mol/L HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, as well as water was added to the flask, followed by ultrasonication to dissolve the reference substance, and then dilution to the mark with the corresponding medium. After shaking well, 5 mL of the solution was precisely measured and transferred to a 100-mL volumetric flask, then diluted to the mark with the same medium. A 50-µL aliquot of each reference solution was injected into the HPLC system ~~continuously for 6 times~~. The retention time of the baclofen main peak, the relative standard deviation (RSD) of the peak area, and the theoretical plate number of the main peak were recorded and analyzed.

The acceptance criteria were the RSD for retention time of the reference solution ($n$ = 6) was less than 1.0%, and RSD of the peak area was less than 2.0%; these indicate suitable stability and precision of the HPLC system.

***Specificity***

Specificity testing was conducted to confirm that blank solvents and excipients did not interfere with the detection of baclofen. To prepare the blank excipient solution and test solution for each medium, blank excipients (same proportion as in baclofen tablets) and five baclofen tablets were placed in separate 250-mL volumetric flasks. Approximately 200 mL of each dissolution medium

was added to the flasks, followed by ultrasonication for 10 minutes to ensure complete dissolution. After cooling to room temperature, the solution was diluted to the mark with the corresponding medium and shaken well. The solution was filtered through a 0.45-µm water-based filter membrane (mixed cellulose membrane, 33-mm diameter); the initial 10 mL of filtrate was discarded to avoid adsorption of baclofen by the filter membrane. A 5-mL aliquot of the subsequent filtrate was transferred to a 10-mL volumetric flask, diluted to the mark with the same medium, and shaken well.

The reference solution was used as the control. A photodiode array (PDA) detector was used to inject 50-µL of blank solvent (dissolution medium), blank excipient solution, reference solution, and test solution into the HPLC system one by one, and the chromatograms were recorded.

To confirm specificity of the method, the acceptance criteria were as follows: blank solvents and excipients did not produce chromatographic peaks that overlapped with the baclofen main peak; the theoretical plate number of the baclofen main peak was not less than 2000; the resolution between the main peak and adjacent peaks was greater than 1.5; the tailing factor of the main peak was not more than 1.5; and the purity angle of the main peak was greater than or equal to the purity threshold.

***Linearity***

Linearity testing was performed to confirm the linear relationship between the concentration of baclofen and the peak area, which is the basis for quantitative analysis. Approximately 20 mg of the baclofen reference substance was accurately weighed, and five portions were prepared. Each portion was placed in a 50-mL volumetric flask, and dissolution medium was added to dissolve the reference substance, followed by dilution to the mark with the same medium (repeated with each medium). After shaking well, these solutions served as linear stock solutions for the different media.

From each stock solution, aliquots of 1, 2, 3, 4, 5, and 6 mL were precisely measured and transferred to six 100-mL volumetric flasks, respectively. Each flask was diluted to the mark with the corresponding medium and shaken well to prepare linear determination solutions (covering a concentration range of 20–120% of the labeled amount of baclofen).

A 50-µL aliquot of each linear determination solution was injected into the HPLC system, and the chromatogram was recorded. Linear regression was performed with the baclofen concentration as the independent variable and the peak area as the dependent variable. A linear correlation coefficient ($R^2$) greater than 0.999 indicates an acceptable linear relationship within the tested concentration range.

***Adsorption of the Filter Membrane***

Filter membrane adsorption testing was conducted to avoid errors in dissolution results caused by adsorption of baclofen by the filter membrane. One baclofen tablet was placed in each dissolution medium. After 30 minutes of dissolution, two identical aliquots from medium collected for testing.

The first part was directly filtered using water-based filter membranes from two manufacturers: polyether sulfone (PES) membranes with a 33-mm diameter (Chongqing Haopu) or 25-mm

diameter (Shanghai Anpu). After discarding the initial filtrate of 2, 5, and 10 mL, the subsequent filtrate was collected for HPLC analysis.

The second part was first filtered through a primary filter head from two manufacturers (Agilent and SOTAX, 10-µm pore size). After discarding the initial filtrate of 2, 5, and 10 mL, the subsequent filtrate was filtered through a secondary filter head (0.45-µm PES membrane, 33- or 25-mm diameter). The initial 2 mL of the secondary filtrate was discarded, and the subsequent filtrate was collected for HPLC analysis.

The peak area of baclofen in each filtrate was measured, and the change in peak area compared to the unfiltered solution was calculated. The acceptance criterion was that all peak area changes were less than 2.0%, confirming that the filter membrane did not adsorb baclofen significantly.

***Accuracy***

Accuracy testing was performed to confirm the recovery of the method, which reflects the reliability of quantitative results. Three different amounts of the baclofen reference substance (approximately 10, 16, and 20 mg, corresponding to 50%, 80%, and 100% of the labeled amount, respectively) were accurately weighed, and three samples were prepared for each amount. Each sample was placed in a 250-mL volumetric flask, and approximately 150 mL of dissolution media was added, followed by ultrasonication to dissolve the reference substance. Blank excipients (in the same proportion as in baclofen tablets) were accurately weighed and added to the volumetric flask. The mixture was sonicated for 10 minutes to ensure uniform mixing, then cooled to room temperature and diluted to the mark with the corresponding medium. After shaking well, the solution was filtered through a 0.45-µm water-based filter membrane (33-mm diameter), and 5 mL of the filtrate was precisely measured and transferred to a 20-mL volumetric flask, diluted to the mark with the same medium, and shaken well to prepare the test solution.

A reference solution was prepared by accurately weighing approximately 20 mg of the baclofen reference substance, placing it in a 50 mL volumetric flask, adding dissolution media for ultrasonication, followed by cooling, diluting to the mark, shaking well, then measuring 5 mL of the solution and transferring it to a 100-mL volumetric flask, and diluting to the mark with the same medium.

A 50-µL aliquot of the reference solution and the test solution was injected into the HPLC system, and the chromatogram was recorded. The recovery was calculated based on the peak area. The acceptance criteria were that recovery of the 50% concentration level was 95–102%; recovery of the 80% and 100% concentrations was 98–101%, and the RSD of nine samples (three concentration levels × three replicates) was less than 5.0%.

***Precision***

Precision testing included repeatability and intermediate measures to confirm the stability of the method under different operating conditions. For repeatability, the reference solution was injected into the HPLC system six times continuously, and the RSD of the peak area was calculated; six samples of the same dissolution solution were also taken, and the RSD of the dissolution rate was measured. The acceptance criterion for repeatability was that the RSD was less than 2.0%.

For intermediate precision, the experiment was conducted by two different operators in the same

laboratory on different days, using different HPLC instruments and dissolution meters. The dissolution rate of baclofen tablets was determined according to the established method, and the RSD of the measurement results for each medium was calculated. The acceptance criteria were that the RSD of the intermediate precision results for each medium was less than 2.0%, and the RSD of 12 samples (six samples for repeatability + six samples for intermediate precision) was less than 5.0%.

***Robustness and Ruggedness***

Robustness testing was performed to evaluate the impact of small intentional changes in method-adjustable parameters on the dissolution determination results in accordance with ICH Q2 guidelines. Two key parameters were investigated: the degassing status of the dissolution medium (degassed vs. non-degassed) and the rinsing volume of the dissolution meter (different volumes). For each adjusted parameter, the dissolution rate of baclofen tablets was determined, and the difference in the average dissolution rate compared to the normal conditions (degassed medium, standard rinsing volume) was calculated. The acceptance criterion was that the difference in the average dissolution rate was less than ± 5%.

Ruggedness testing was conducted to verify the inter-instrument consistency of the established dissolution method by comparing dissolution results from different brands of fully automatic dissolution testers (Agilent 708-805DS and SOTAX). The dissolution curves of baclofen tablets were determined using the two instruments under the same experimental conditions, and the average cumulative dissolution rate differences at each sampling time point were calculated. The acceptance criteria were that the difference in the average cumulative dissolution rate at the time point after 15 minutes was less than ± 10%, and the difference at the standard sampling points and subsequent points was less than ± 5%.

***Sample and Standard Solution Stability***

Solution stability testing was conducted to confirm the stability of the reference solution and test solution during storage, avoiding errors caused by solution degradation.

Each reference solution (prepared with each dissolution medium) was stored at room temperature for 24 hours. The test solution was prepared according to the dissolution method, stored at 37 °C for 1 hour (simulating the dissolution process), then transferred to room temperature for storage for 24 hours. At 0, 2, 4, 8, 12, and 24 h, a 50-µL aliquot of each solution was injected into the HPLC system, and the peak area was recorded. The change in peak area compared to the 0 h value was calculated, with an acceptance criterion of less than 2.0%.

**Dissolution Testing**

To compare the in vitro dissolution behavior of generic and original baclofen tablets, dissolution tests were conducted on three batches of generic preparations and three batches of original preparations. For each batch, 12 tablets were randomly selected to ensure the representativeness of the sample.

Four dissolution media (0.01 and 0.1 mol/L HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) were used, each with a volume of 500 mL. Samples were collected at 5, 10, 15, 30, 45, and 60 min. After sampling, the same volume (and temperature) of dissolution medium was

immediately added to the vessel to maintain a constant volume, ensuring the accuracy of the dissolution rate calculation.

The collected samples were filtered through a 0.45-μm filter membrane (after discarding the initial filtrate), and the filtrate was analyzed by HPLC to determine the concentration of baclofen. The cumulative dissolution rate of each tablet was calculated based on the concentration, and the average cumulative dissolution rate and RSD of 12 tablets in each batch were further calculated.

The sampling method was optimized to reduce errors: the sample volume was 1.5 mL, the membrane moistening and washing volume was 10 mL, the washing volume was 5 mL, the waste volume was 0.5 mL, and the replenishment volume was 2 mL. For the Agilent 708 + 850S automated dissolution tester, a rinsing volume of 20 mL was used, which was verified to improve the uniformity of the test results compared to a 10 mL rinsing volume (no significant difference in the dissolution rate was observed between the two volumes, with the absolute difference in average cumulative dissolution rate < 3.0% at all time points). Notably, the automated sampling system of the instrument replenishes an equal volume of preheated dissolution medium immediately after rinsing, maintaining a constant total volume of the dissolution medium (500 mL) throughout the test, thus eliminating the risk of excessive dilution caused by the 20-mL rinsing volume. A 10-mL rinsing volume was only used for dissolution curve tests with short sampling intervals as a precautionary measure to avoid any potential dilution risk.

### Data Analysis

All experimental data were processed using Microsoft Excel 2016 to ensure the accuracy and traceability of the data. The dissolution results were presented as the percentage of cumulative drug release, with the mean or median used to represent the central tendency and the RSD used to represent the dispersion degree.

For the comparison of dissolution curves between generic and original preparations, the similarity factor ($f_2$) was used as the evaluation index. An $f_2$ value greater than 50 indicated that the dissolution curves of the two preparations were similar, confirming that the in vitro drug release behavior of the generic preparation was consistent with that of the original preparation.

## RESULTS

### Solubility of Baclofen API

The solubility of baclofen was 28.0 mg/mL in 0.1 mol/L HCl (pH 1.0), 7.0 mg/mL in 0.01 mol/L HCl (pH 2.0), 5.4 mg/mL in pH 4.5 acetate buffer, 4.7 mg/mL in water (pH 6.39), and 4.9 mg/mL in pH 6.8 phosphate buffer, indicating pH dependence. Additionally, the volume of medium required to dissolve the maximum daily dose of 100 mg varied with pH, being 3.6, 14.3, 18.5, 21.3, and 20.4 mL in 0.01 mol/L HCl, 0.1 mol/L HCl, pH 4.5 acetate buffer, water, and pH 6.8 phosphate buffer medium, respectively.

### Method Validation

The dissolution method passed all validation requirements in all media. The method exhibited excellent specificity (no interference from blank solvents or excipients), linearity (correlation coefficient r ≥ 0.999), accuracy (recovery rates 95%–101%), precision (RSD < 2.0%), and

robustness (stable results under normal operating parameters), with negligible filter membrane adsorption and 24-hour solution stability. Results of the method validation are available as supplemental material.

For the robustness tests, when the dissolution medium was not degassed, the dissolution of two tablets was below the limit, indicating that the medium not being degassed might affect the dissolution measurement. Therefore, the medium should be degassed during the dissolution measurement, and the volume of the dissolution medium should be accurately measured. The dissolution results did not meet the requirements when the rinse volume was 5 mL, and the average dissolution difference compared with normal conditions was greater than 5%, indicating that the rinse volume of 5 mL affected the dissolution measurement results. Except for the above conditions, the dissolution deviations were all less than 5% under different rinse volumes (8–10 mL for Agilent automatic dissolution apparatus), indicating that the dissolution method had acceptable robustness.

**Dissolution**

The mean cumulative dissolution rates of the three batches of generic preparations (including the BE batch) and several batches of reference preparations in 0.01 and 0.1 mol/L HCl for 15 minutes were all not lower than 85%.

In pH 4.5 acetate buffer, mean cumulative dissolution of two generic preparations (190803 [BE batch] and 190805) and two reference preparations (TM629 [BE batch] and TV911) were all not lower than 85%; the other generic (190804) and reference (TL641) batches were lower than 85% but not lower than 80%, and the differences in mean cumulative dissolution at each time point between these two batches were all within 5%.

In pH 6.8 phosphate buffer, the uniformity of the generic preparations and the reference preparations was slightly poor and did not meet the requirements for $f_2$ calculation; however, mean cumulative dissolution all three generic preparations and the BE batch reference preparation (TM629) were less than 10% at 5 minutes and less than 5% at 10 minutes and later time points. The dissolution curves of the generic preparations and the reference preparations can be considered as similar (Fig. 1).

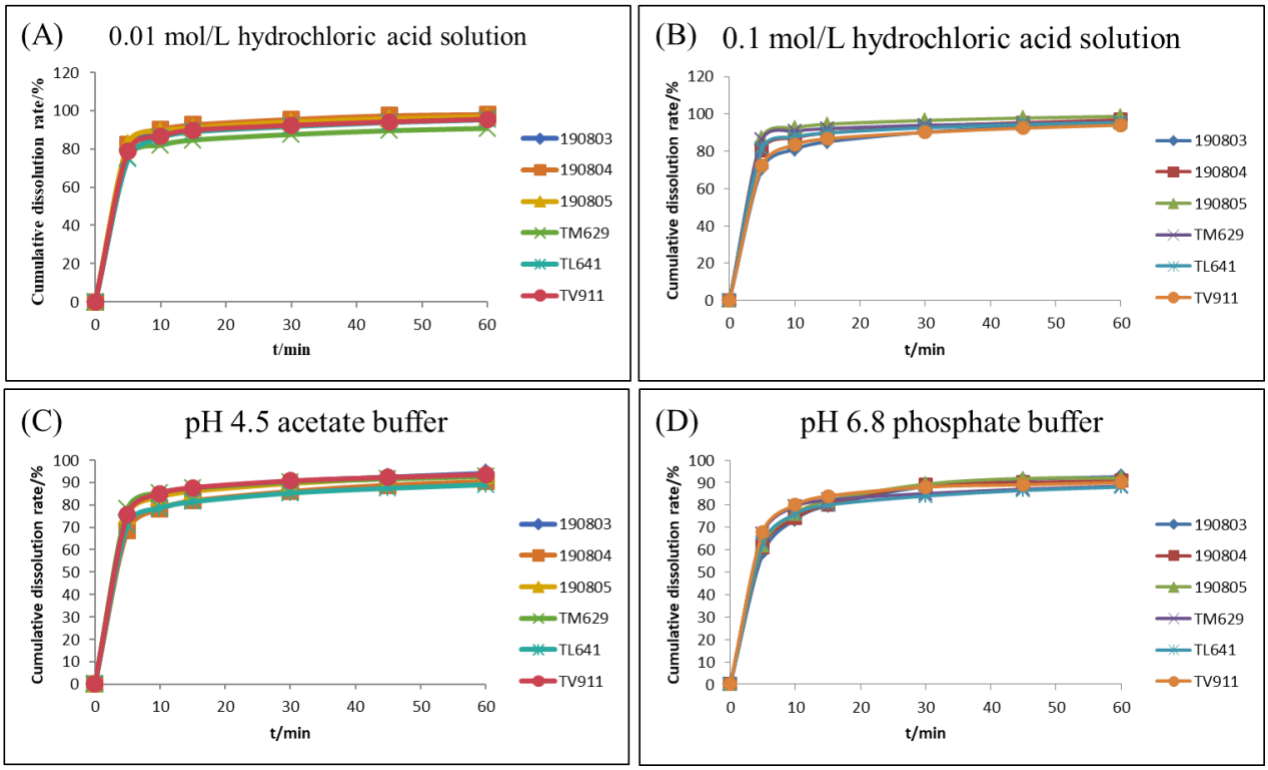


*Figure 1. Dissolution curves of baclofen tablets in four different media.*

## DISCUSSION

As shown in the solubility test results of baclofen API, baclofen exhibits obvious pH-dependent solubility, with significantly higher solubility in strong acidic media and relatively low solubility in weakly acidic and neutral media. This pH-dependent solubility characteristic directly leads to the medium-dependent dissolution behavior of baclofen tablets, which is consistent with prior findings that baclofen achieves rapid and complete dissolution in acidic media but slower, more variable release in neutral environments. This property is clinically relevant because patients' gastrointestinal environments—such as gastric acid concentration altered by age, concurrent medication use, or underlying gastrointestinal conditions—can directly affect the in vivo dissolution and subsequent bioavailability of baclofen tablets. For instance, elderly patients with reduced gastric acid secretion or those taking proton pump inhibitors may experience delayed dissolution of baclofen in the neutral upper gastrointestinal tract, potentially leading to lower peak plasma concentrations and diminished spasticity-relieving efficacy. Thus, the study's focus on evaluating dissolution profiles across four key media (0.01 mol/L HCl, 0.1 mol/L HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer)—which simulate the physiological pH gradient from the stomach to the small intestine—effectively bridges the gap between in vitro dissolution data and in vivo therapeutic performance.

### HPLC Dissolution Method

The HPLC-based dissolution method developed in this study was optimized based on a comprehensive analysis of global pharmacopoeial standards. While six major pharmacopoeias

(ChP, USP, BP, JP, KP, IP) uniformly adopt the paddle method at 50 rpm for baclofen dissolution testing, they differ significantly in media type, volume, detection technique, and sampling time. This study selected 500 mL as the medium volume (consistent with ChP, USP, JP, KP) and 265 nm as the detection wavelength (aligned with ChP, USP, BP), balancing standardization and practicality. The choice of HPLC over UV spectrophotometry (used by JP, KP) was driven by baclofen's low specification, as HPLC offers enhanced specificity and avoids interference from excipients— an advantage verified by the specificity test, where blank solvents and excipients showed no chromatographic interference with baclofen.

Method validation results further confirm the reliability of the established approach. The method exhibited excellent linearity ($r \geq 0.999$ across all media), negligible filter membrane adsorption (peak area change < 2.0% after discarding 5 mL initial filtrate), and acceptable accuracy (recovery rates within 95–101%). Notably, robustness testing identified critical parameters: a rinse volume of 5 mL led to non-compliant dissolution results (average dissolution difference > 5% vs. normal conditions), while degassing of the dissolution medium and accurate volume measurement were essential to avoid variability. These findings provide actionable guidance for routine quality control of baclofen tablets, ensuring that minor deviations in operating parameters do not compromise the accuracy of dissolution data.

**Dissolution Curve Similarity**

The similarity of dissolution curves between the generic baclofen tablets and the reference listed drug (RLD) is a key indicator of in vitro equivalence, which is closely linked to BE. In acidic media (0.01 and 0.1 mol/L HCl), both preparations achieved > 85% cumulative dissolution at 15 minutes, indicating rapid dissolution under gastric pH conditions—this ensures that baclofen is quickly released in the stomach, laying the foundation for timely absorption. In pH 4.5 acetate buffer (simulating the gastric outlet and upper small intestine), most batches of generics and RLD also reached > 85% dissolution, with differences between the two preparations < 5% at all time points, reflecting consistent dissolution behavior in the transition from acidic to neutral environments.

A minor challenge emerged in pH 6.8 phosphate buffer (simulating the distal small intestine), where both generics and RLD showed slightly poor uniformity, failing to meet the initial $f_2$ factor calculation requirements. However, the mean cumulative dissolution difference between the generic batches and the RLD's BE batch (TM629) was < 10% at 5 minutes and < 5% at 10 minutes and later time points—values that still support practical equivalence. This slight uniformity issue may be attributed to the lower solubility of baclofen in neutral media, which amplifies small variations in tablet formulation (e.g., excipient particle size, compression force). Nevertheless, the overall similarity across all four media confirms that the generic preparation's dissolution behavior is consistent with the RLD, reducing the risk of clinical efficacy fluctuations between the two.

**Limitations and Future Directions**

One limitation of this study is the exclusion of water as a dissolution medium for curve comparison, despite its inclusion in method validation. Water (used by JP, KP as the dissolution medium) simulates extreme neutral conditions (e.g., severe hypochlorhydria), and future studies could incorporate water to further evaluate dissolution consistency under such scenarios.

Another consideration is the global regulatory differences in dissolution testing. For example, the United States Food and Drug Administration and Chinese National Medical Products Administration may have varying requirements for dissolution medium selection and $f_2$ factor application for muscle relaxants like baclofen. Future research could compare these regulatory frameworks to provide a more comprehensive reference for the international registration of generic baclofen tablets.

**Clinical and Industrial Significance**

From a clinical perspective, the consistent dissolution behavior of the generic and RLD baclofen tablets supports the safe substitution of the generic for the RLD. Given that baclofen is a first-line long-term treatment for neurological spasticity (e.g., spinal cord injury, multiple sclerosis), reliable generic alternatives can improve drug accessibility and reduce treatment costs for patients—addressing unmet needs in the management of chronic neurological conditions.

For the pharmaceutical industry, this study demonstrates a systematic approach to generic drug development. By aligning method development with global pharmacopoeial standards, conducting rigorous method validation, and using $f_2$ factor analysis to confirm dissolution similarity, manufacturers can streamline the development process and ensure compliance with regulatory requirements. The findings also highlight the importance of optimizing critical parameters (e.g., rinse volume, medium degassing) in dissolution testing, which can serve as a reference for the development of other oral solid dosage forms with medium-dependent dissolution properties.

## CONCLUSION

This study systematically established and validated an HPLC-based in vitro dissolution determination method for baclofen tablets and compared the dissolution curve consistency between generic preparations and the RLD across key physiological media. Results of the method validation confirmed that the method is reliable, sensitive, and suitable for the quantitative determination of baclofen tablet dissolution, providing a standardized technical tool for in vitro quality evaluation of baclofen tablets. Regarding dissolution curve comparison, the generic baclofen tablets showed consistent dissolution behavior with the RLD. This indicates that the generic preparation has similar in vitro release characteristics to the RLD, laying a solid foundation for ensuring consistent in vivo bioavailability and clinical therapeutic effects.

This study not only provides a scientific reference for the BE research and market approval of generic baclofen tablets but also contributes to improving the accessibility of high-quality baclofen preparations, thereby better meeting the long-term treatment needs of patients with neurological spasticity (such as spinal cord injury and multiple sclerosis) and promoting the standardized development of the generic drug industry for central muscle relaxants.

## DISCLOSURES

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## SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

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